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review

Adjuvant treatment of breast cancer patients with trastuzumab

Erika Matos, Tanja Čufer

Institute of Oncology Ljubljana, Department of Medical Oncology, Ljubljana, Slovenia

Background. *Trastuzumab is a monoclone antibody directed against HER2 receptors that are overexpressed in approximately 20% of breast cancer patients. The present paper presents five clinical trials in which trastuzumab was applied in breast cancer patients in adjuvant setting. The results of all the trials consistently demonstrate a high efficacy of this target drug in the patients with HER2 positive tumours. So far, no formal guidelines for using trastuzumab in adjuvant setting for breast cancer have been approved. The reasons are many: (i) mean observation time in the studies done so far was considerably short; (ii) the drug was used according to different schedules, (iii) the overall time of treatment with trastuzumab was different in each trial, (iv) late side effects of treatment with trastuzumab are inadequately investigated, and (v) nobody can so far say for sure for which HER2 status patients therapy with trastuzumab is really beneficial.*

Conclusions. *Trastuzumab is definitely very helpful in the treatment of the HER2-positive breast cancer patients that are hormone-independent and of anatomically larger tumours; but, what the absolute benefit of trastuzumab therapy in the treatment of small hormone-dependent tumours is remains a mystery. Incidentally, it must be borne in mind that cardiotoxicity, the well known side effect, may put particularly elderly patients at risk of death, thus beating any treatment advantages down. It has also not been yet resolved at what time it would be most appropriate to start with the therapy with trastuzumab, what would be the optimal duration of the therapy and whether trastuzumab is to be administered concurrently with chemotherapy or immediately after it? What is the optimal treatment duration, one or two years or only a few months? In addition there is still a question of optimal HER2 status determination and which HER2 status predicts for trastuzumab benefit. These questions will hopefully be answered after a longer observation time of the patients included in five clinical trials that are discussed in the article.*

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Correspondence to: Erika Matos, M.D., Institute of Oncology Ljubljana, Zaloška 2, SI-1000 Ljubljana, Slovenia; Phone: +386 1 5879 284; Fax: +386 1 5879 400; E-mail: ematos@onko-i.si

Introduction

Breast cancer is the most frequent malignant disease in women. Given the clinical course, this disease is very diverse. It has now been known for some time that breast cancer may be hormone-dependent or in-

dependent and that this characteristic is one of the crucial in the course of the disease and its treatment. After recognizing new molecular characteristics of tumour cells, the diversity appears to be even greater. Tumour cell membranes as well as the inside of cells are populated with different proteins that are incorporated in the signal paths controlling the cell growth and reproduction. One of these proteins is HER2, a receptor for human epidermal growth factor. The tumours with overexpressed receptor HER2 are referred to as HER 2 positive tumours, which represent approximately 20% of all breast cancers. These tumours are biologically more aggressive. At the time of disease detection, they are usually larger than HER2 negative tumours, very often axillary lymph nodes are already involved, and in non-treated patients, the time interval to the disease recurrence is usually shorter.[1] According to recent results, these tumours are highly sensitive to anthracylines, whereas their sensitivity to hormonal therapy is less explicit. Approximately 50% of HER2 positive tumours are hormone-dependent; however, it seems that the hormonal therapy is less efficient in patients with these tumors.[1-3]

HER2 status can be determined by immunohistochemistry (ICH) or by fluorescence in situ hybridization (FISH). The former determines the quantity of HER2 protein in a cell membrane, and the latter, the HER2 gene amplification.[1]

The prognosis of the HER2-positive breast cancer patients improved significantly with the introduction of HER2-targeted agent, namely trastuzumab, in the treatment. Trastuzumab is a recombinant monoclonal antibody directed against HER2 receptor. Trastuzumab first proved to be effective in the treatment of patients with advanced breast cancer and overexpression of HER2 receptors.[4,5]

The binding of trastuzumab to HER2 receptor inhibits the signal pathways inside a tumour cell, which are essential for a cell growth, reproduction and distant metastatic spread. Trastuzumab, applied as monotherapy or in combination with cytostatics, significantly increases the survival of patients with HER2 positive metastatic breast cancer and improves disease control.[4,5] Unfortunately, metastatic breast cancer is still incurable disease. Trastuzumab was found to be effective in patients with overexpressed HER2 receptor, determined positive either immunohistochemicaly (IHC 3+) or by FISH. If IHC score is 2+, FISH test should be performed in order to determine HER2 status.[6]

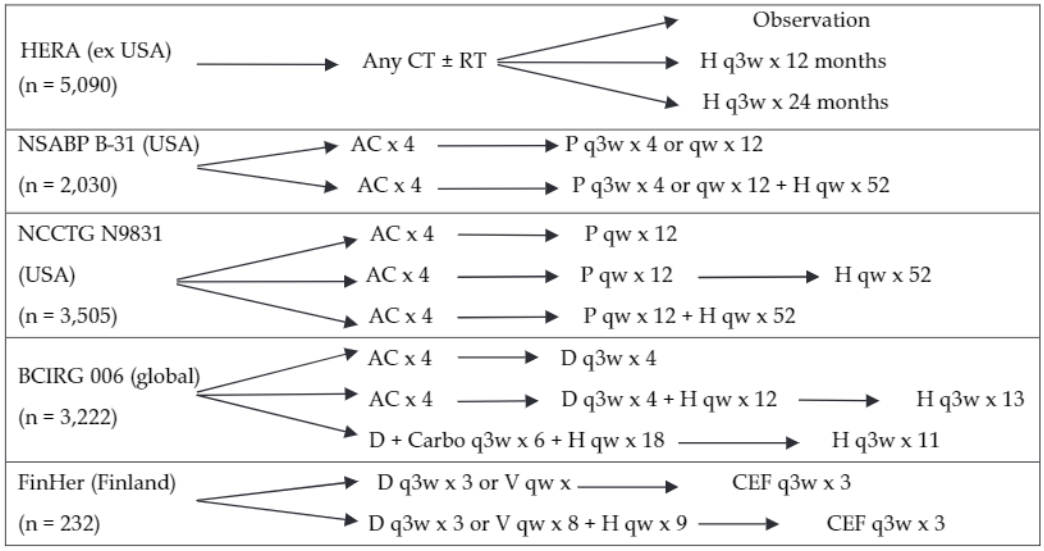
In addition to trastuzumab, targeting selectively HER2 receptor, some new target drugs are already in pre-clinical and clinical trials; according to the results of clinical trials, some have already proven to be effective in the treatment of HER2 positive breast cancer patients. One of these drugs is lapatinib, a small molecule inhibiting not only HER2 but also HER1 receptor.[1]

The role of trastuzumab in adjuvant therapy

High efficiency of trastuzumab in the treatment of metastatic breast cancer motivated researchers to further investigate the drug and use it in adjuvant setting.

So far, five big prospective clinical trials in which trastuzumab was applied as adjuvant therapy have been performed. Over 13,000 patients were included in these trials, all investigated trastuzumab applied in combination with cytostatics. The trials were carried out according to different treatment schedules (Table 1). In the HERA trial patients were administered trastuzumab only after completed adjuvant cytostatic treatment. This was the three arm trial: (i)

Table 1. Trastuzumab adjuvant trials designs



the treatment arm without trastuzumab – the comparison arm, (ii) the treatment arm with one-year trastuzumab therapy, and (iii) the treatment arm with two-year trastuzumab therapy. So far, only the results of the second arm are available, *i.e.* of one-year therapy with trastuzumab, while the results of the two-year therapy are awaited and will hopefully be available next year.[7] In both American trials (NSABP-B31 in NCCTG N9831), the patients first received chemotherapy according to AC schedule (adriablastin, cyclophosphamide), and continued with a weekly or three-weekly paclitaxel. Trastuzumab was added to paclitaxel, and after completing cytostatic therapy, the patients were receiving it as monotherapy for one year.[8,9] In the BCIRB 006 clinical trial, the patients were first treated with 4 cycles of chemotherapy according to AC schedule, followed by docetaxel with or without the addition of trastuzumab, which they were receiving for one year. The third treatment arm in BCIRG 006 was non-anthracycline one; the patients in this arm were treated with a combination of docetaxel and carboplatin to which trastuzumab was added at the very start of the therapy. The patients from this treatment arm were treated with trastuzumab for one year as well. In contrast to the two American trials in which the patients were receiving trastuzumab in weekly doses, the patients of the BCIRG 006 trial started the therapy with weekly doses of trastuzumab and were receiving it in these doses as long as they were receiving also docetaxel; after completing chemotherapy with docetaxel, they were receiving it in 3-weekly schedule.[10] The Finnish trial FinHER was slightly different from all the others. The patients received only nine weekly infusions of trastuzumab in combination with taxanes or vinorelbine, and after that the treatment with anthracyclines was following.[11]

Patients' selection

The treatment schedules in the above trials were different, but the inclusion criteria were very similar. The criterion that was common to all trials was the requirement that the patients had the HER2 positive tumour surgically removed. Another in-

clusion criterion was normal LVEF (left ventricular ejection fraction) and absence of any serious cardiologic morbidity. The trials were conducted on the patients with positive as well as those with negative axillary lymph nodes. The lowest percentage of node-positive patients (57%) was included in the HERA trial and the highest (89%) in the FinHER trial. The patients with node negative disease were also included in the trials provided that they had at least one additional unfavourable prognostic factor. This additional prognostic factor was the size of the tumour that, in HERA trial, had to be larger than 1 cm [7], whereas in the American trials, it had to be larger than 2 cm and/or 1 cm provided that the tumour was hormone-independent.[8] For the inclusion in the BCIRG 006 trial, the size of the tumour had to be larger than 2 cm; if it was smaller, it had to be hormone-independent or purely differentiated or diagnosed in a patient aged less than 35 years.[10] The Finnish trial included patients with tumours larger than 2 cm or if smaller those with negative progesterone receptors.[11] The patients with hormone-dependent as well as those with hormone-independent tumours were included in the above trials. The lowest percentage of patients with hormone-independent tumours was included in the Finnish trial (47%) and the highest in the BICRG 006 trial (54%).

Table 2. Efficacy of trastuzumab in adjuvant setting

1.) NSABP B31/NCCTG 9831 (MFU 3 years)		
DFS	HR = 0.49	p = 0.001
OS	HR = 0.63	p < 0.004
2.) HERA (MFU 2 years)		
DFS	HR = 0.64	p < 0.0001
OS	HR = 0.66	p < 0.0115
3.) BCIRG 006 (MFU 3 years)		
AC → TH		
DFS	HR = 0.61	p < 0.0001
OS	HR = 0.67	p < 0.004
TCH		
DFS	HR = 0.59	p = 0.0003
OS	HR = 0.66	p = 0.017
4.) Fin-HER (MFU 3 years)		
RFS	HR = 0.42	p = 0.01
OS	HR = 0.41	p = 0.07

DFS - disease-free survival
OS- overall survival
RFS - relapse-free survival
MFU - median follow up

Results – efficacy of trastuzumab applied in adjuvant setting

Despite different treatment schedules, the results of these trials were remarkably consistent. They definitely proved that the addition of trastuzumab to the cytostatics remarkable increases the likelihood of cure of the patients with operable HER2-positve breast cancer.

After a mean observation time of more than three years, it was noted that the use of trastuzumab decreased the risk of recurrence by approximately 50% (HR range 0.42 – 0.64) and the risk of death by approximately 40% (HR range 041 – 0.66). The differences in the disease-free survivals and overall survivals were highly statistically significant in all trials (Table 2). The addition of trastuzumab has a favourable effect regardless of the concomitantly applied cytostatic therapy. A statistically significantly improved disease-free survival and overall survival were reported also in the patients who were treated with non-anthracycline adjuvant therapy.[10] And, to our surprise in Finnish trial merely a nine-week therapy with trastuzumab improved significantly both the disease-free survival and overall survival at same extend as one year therapy in other trials.[11]

Table 3. Relative and absolute benefit of adjuvant trastuzumab according to hormonal status of tumor and anatomical spread of the disease

	Relative risk for relapse * – HERA trial (oral presentation: Gelber; SABCS 2005) (12)		Estimation of absolute benefit **	
	ER in PR neg.	ER in/ali PR poz.	ER in PR neg.	ER in/ali PR poz.
N≥4	33%	33%	16%	16%
N1-3	25%	12%	12%	6%
N0	18%	10%	9%	5%

* median observation time of 1 year

** 50%-reduced risk of relapse was estimated from the results of the above trials (8,9,10,11) with a mean observation time ranging 1-3 years. The analysis of the results showed a 40-50% relative risk reduction.

Patients' subgroup particularly benefiting from the treatment with trastuzumab

According to the results presented, trastuzumab is effective for all HER2 positive breast cancer patients, irrespective of anatomical stage (tumour size, nodal status) and of hormonal receptor status.[7,8]

Today, it is generally accepted treatment for HER2 positive early breast cancer patients. The data analysis of the HERA trial presented by Gelber at SABCS in 2005 showed that the absolute benefit was varied.[12] The patients with hormone-independent tumours or anatomically amply spread disease are benefiting more from the treatment with trastuzumab. And what is also very important that the significance of hormone-dependency diminishes with the increasing spread of the disease (Table 3).

HER2 status determined by IHC or FISH seems to be a reliable parameter for selecting metastatic breast patients who may benefit from trastuzumab therapy. But it is not known if HER2 status determined by these two methods defines well a group of patients who may benefit from adjuvant trastuzumab. A study presented at last ASCO meeting showed that a significant proportion of patients with HER2 negative tumours benefited from adjuvant trastuzumab. At the time being we are still not sure if HER2 status as it is defined now is a good predictor of benefit from adjuvant trastuzumab.[13]

Significance of early start of treatment with trastuzumab

At present, it is believed that the patients with HER2-positive tumours should start the adjuvant therapy with trastuzumab as early as possible. The above suggestion was confirmed also by the analysis of 1682 patients included in the clinical trial N9831 that compared the survival of the patients who received trastuzumab after the completed treatment with cytostatics and the survival of patients who started the therapy with trastuzumab concomitantly with paclitaxel. The latter patients who received trastuzumab earlier, *i.e.* concomitantly with paclitaxel, had significantly better survival (HR 0.63).[8]

Safety of treatment with trastuzumab

In all trials performed on trastuzumab, cardiotoxicity appears to be to the most severe side effect. From the studies on the patients with disseminated disease, it could be assumed that the combination of anthracyclines and trastuzumab, though considered to be a highly effective combination, was

Table 4. The risk of heart failure in patients treated with adjuvant trastuzumab: depends upon the age of a patients, heart function and previous anthracycline-based chemotherapy

		Age (years)	
		<50	≥50
LVEF (%) after AC (7)	50-54	3/48 (6.3%)	9/47 (19.1%)
	55-64	5/229 (2.2%)	10/194 (5.2%)
	65+	1/160 (0.6%)	2/159 (1.3%)

p (age) = 0.04, p (LVEF) < 0.0001

severely cardiotoxic. A concomitant application of both agents is therefore unacceptable in routine clinical practice. An independent analysis of cardiotoxic effects was made on 837 patients included in the trial NSABP-B31 and, from the analysis of results it was concluded that the risk for cardiotoxicity correlated with the age of patients at first administration of trastuzumab and with the functional performance of the heart assessed before treatment by the LVEF. Undesired treatment effects may be expected to be more frequent in the patients aged over 50 years and in those with lower starting LVEF. Patients with heart failure or poor functional performance of the heart were not included in the analysis (Table 4). However, it remains unclear to what extent cardiotoxicity is due to trastuzumab and to what extent to an earlier therapy with anthracyclines. An interesting conclusion drawn from the results of the trial BCIRG 006, which studied cardiotoxic side effects, was that cardiotoxicity significantly increased if trastuzumab was used after the anthracycline based chemotherapy; but, it did not appear after non-anthracyclne based chemotherapy.[14]

Other side effects of treatment, often mentioned in the studies, are also hypersensitive reactions. Severe allergic reactions *e.g.* drop of blood pressure or bronchospasm, are very rare. The pyrogene reactions unique associated with the first drug administration are more frequent. They usually appear in app. 30% of patients. Pneumonitis is also a possible, but rather rare undesired effect with the incidence of approximately 0.2% (4). So far, no firm data is available about possible late side effects of treatment with trastuzumab.

Conclusions

Trastuzumab, an inhibitor of HER2 receptor, is definitely a very effective drug for the treatment of a selected group of patients with HER2 positive breast cancer. Five large clinical trials including more than 13.000 patients uniformly confirmed the beneficial role of trastuzumab in terms of disease free survival and overall survival in all HER2 positive patients. However, the role of trastuzumab in the adjuvant therapy has not been precisely determined and the guidelines for its use have not been generally approved yet. A number of questions remain unanswered, *e.g.*: What would be the optimal treatment duration? When should it be optimal to start the therapy with trastuzumab? In which combination with cytostatics would it be optimal? When should the combination with anthracycline be applied? Which patients would be likely to benefit optimally from the treatment with trastuzumab? How to prevent undesired cardiotoxic effects of the drug? What are late side effects of treatment with trastuzumab? We believe that these questions will be answered

after a longer observation time and thorough follow-up of the patients treated with trastuzumab and included in the described clinical trials performed to prove the efficiency of trastuzumab in adjuvant setting. Only a careful observation and follow-up of patients treated with trastuzumab by experienced therapists will present benefits of such treatment for each patient individually and thereby also to other potential patients. Undoubtedly, trastuzumab is a very promising drug for a selected group of HER2 positive breast cancer patients. In addition, there are new target drugs in development. Among the drugs for treating HER2-positive breast tumours, the most promising seems to be lapatinib, a dual inhibitor of both HER1 and HER2 receptors. What will be the optimal role of trastuzumab as well as of a few dozens of other target drugs that are being tested is not yet known; but, the drug trastuzumab was the first that proved (i) that the targeted therapy is far more efficient than the empiric treatment with cytostatics, in particular when it is applied in an early stage of the disease, that means in adjuvant setting, and (ii) that the targeted therapy, if properly chosen and managed, will improve overall survival and disease control rates in breast cancer patients.

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